# AFFECTIVE MEASURES OF ANGER AND HOSTILITY AND BRACHIAL ARTERY ENDOTHELIAL FUNCTION DURING MENTAL STRESS AND FOREARM OCCLUSION

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## ABTRACT

Title of Thesis: Affective Measures of Anger and Hostility and Brachial Artery Endothelial Function during Mental Stress and Forearm Occlusion

Melissa Kay McCeney, Master of Sciences, 2001

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Mental stress triggers myocardial ischemia in patients with coronary artery disease, and may involve impaired functioning of the endothelial lining of coronary blood vessels. The present study examined the effects of hostility and mental stress on flow-mediated brachial artery dilation using 2D echocardiography in 11 men and 17 women. Brachial artery diameter was measured before and after 4 minutes of forearm arterial occlusion by pneumatic cuff, mental stress induced by a public speaking task or mental arithmetic with harassment, a mental stress task combined with forearm occlusion, and administration of sublingual nitroglycerin. Brachial artery diameter increased significantly during all interventions. Brachial artery vasodilation during occlusion + mental stress was significantly reduced in participants with high Hostile Affect. Vasodilation during the combined condition was similarly associated with Anger-Hostility. Affective measures of anger and hostility were associated with impaired endothelial responses to hyperemia and mental stress.

Affective Measures of Anger and Hostility and Brachial Artery Endothelial Function during Mental Stress and Forearm Occlusion

by

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Master's Thesis submitted to the Faculty of the Department of Medical and Clinical Psycholgoy Graduate Program of the Uniformed Services University of the Health Sciences in partial fulfillment of the requirements for the degree of Master of Science

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In the last twenty years, the role of vascular endothelium has become a major research topic in physiology, cardiology, and psychology. Vascular endothelium lines the inside of blood vessels and envelops circulating blood in a continuous layer of cells. Interest in vascular endothelium first developed when scientists noted heterogeneity in the effects of various vasoactive drugs on blood vessels. For example, in *in vitro* studies, arterial segments would sometimes dilate in response to acetylcholine and would other times constrict (e.g., DeMay & Vanhoutte, 1982). Furchgott and Zawadzki (1980) demonstrated that the reason for this inconsistency was that the endothelial layer was sometimes damaged when the vessel was removed and prepared for *in vitro* study, and that blood vessels responded differently to the same vasoactive substances depending on whether or not the endothelial layer was intact. It has since been demonstrated that arteries dilate in response to acetylcholine, substance P, ATP, bradykinin, and other substances, but only if the endothelium is present (Cocks & Angus, 1983; Furchgott, 1983). Vasoconstrictive substances, including norepinephrine and serotonin, are significantly more powerful in the absence of the endothelium (Cocks & Angus, 1983) and may even limit constriction or cause dilation when the endothelium is present (Gordon, et al., 1989). The response of vascular smooth muscle and that of the endothelium interact to "counterbalance" the vessel response to vasoactive stimuli (Furchgott, 1983). Constrictor (e.g., epinephrine, norepinephrine) amines cause the release of a vasodilator substance or substances from endothelial cells that act as a physiological antagonist of smooth muscle contractile responses (Cocks & Angus, 1983).

Nitric oxide is now known to be the primary source of endothelial-dependent relaxation. Nitric oxide is a vasodilating molecule synthesized from L-arginine and released from endothelial cells to act as a local regulator of vascular tone (Dietz, Rivera,

Eggener, Fix, Warner, & Joyner, 1994). Because of its metabolic function with regard to vasoactive substances, vascular endothelium has been described as a highly active metabolic and endocrine organ in its own right (Vane, Anggard, & Botting, 1990).

Endothelial Function and Atherosclerosis. It has since been demonstrated that endothelial function can be lost *in vivo* due to injury to the endothelium, as in the case of atherosclerosis (Ross, 1986) or the presence of coronary risk factors (e.g., Celermajer, et al., 1992). When endothelial function is lost, the release of nitric oxide is impaired, and the normal response to vasodilator stimuli is replaced by attenuated dilation, and eventually, paradoxical vasoconstriction (Ludmer, et al., 1986). Paradoxical vasoconstriction has been shown to occur in atherosclerotic arteries in response to catecholamines (Ludmer, et al., 1986; Vita, et al., 1990), increased heart rate (Nabel, Selwyn, & Ganz, 1990), the cold pressor test (Nabel, Ganz, Gordon, Alexander, & Selwyn, 1988), and exercise (Gage, et al., 1986). In a study by Ludmer and colleagues (1986), angiographically normal coronary arteries dilated in a dose-dependent fashion to acetylcholine, but there was dose-dependent constriction in stenotic, pre-stenotic, and post-stenotic arterial segments. In five participants in that study, there was sufficient constriction in response to acetylcholine to cause temporary coronary occlusion. These same stimuli result in dilation in normal arteries, and the constriction that occurs in injured arteries can be reversed by nitroglycerin, which acts directly on the smooth muscle wall in a non-endothelial dependent manner (Gage, et al., 1986). The fact that these injured arteries dilate in response to nitroglycerin indicates that the failure to dilate properly is the result of endothelial dysfunction and not a failure of the smooth muscle of the arterial wall.

Endothelial dysfunction begins as a localized process. In patients with mild to

moderate coronary artery disease, acetylcholine may elicit heterogeneous responses (i.e., both constriction and dilation) in different segments of the same coronary artery (Penny, et al., 1995; El-Tamimi, et al., 1994) or peripheral artery (Testa, et al., 1996). In the early stages of atherosclerosis, L-arginine attenuates acetylcholine-induced vasoconstriction in diseased coronary arteries. However, L-arginine has no effect on paradoxical constriction in severely diseased arteries (Otsuji, et al., 1995).

Inappropriate vasoconstriction is of particular concern when it occurs in coronary arteries. For example, vasoconstriction during exercise in diseased coronary arteries could further limit myocardial oxygen supply, especially if it occurs in the presence of coronary artery stenosis (Gordon, et al., 1989).

Vascular endothelium is abnormal in the earliest stages of atherosclerosis before the development of plaques (Ross, 1986) and has even been described as the initiating event in atherosclerosis (Anderson, 1999). Endothelial injury predisposes an individual to thrombosis, leukocyte adhesion, and proliferation of smooth muscle cells in the arterial wall (Ross, 1986). Impaired endothelial dependent relaxation has been documented in animals and humans with hypertension and atherosclerosis (Vanhoutte, 1988; Panza, Quyyumi, Brush, & Epstein, 1990; Gordon, et al., 1989).

Endothelial Function and Cardiovascular Risk Factors. Endothelial dysfunction is also associated with risk factors for coronary artery disease (CAD). Vita et al. (1990) determined that vasoconstrictor responses to acetylcholine are independently associated with increasing serum cholesterol, male gender, positive family history for coronary artery disease, and increasing age. Impaired endothelial function can be seen in asymptomatic children with a positive family history for atherosclerosis as young as eight years old (Celermajer, et al., 1994). Cigarette smoking also potentiates endothelial

dysfunction, perhaps via oxidized LDL cholesterol (Heitzer, et al., 1996). Multiple coronary risk factors have a cumulative negative effect on endothelial function (Seiler, Hess, Buecchi, Suter, & Krayenbiehl, 1993). In fact, in some studies, the best predictor of endothelial dysfunction is the number of coronary risk factors a person has (e.g., Vita et al., 1990). However, despite the overall correlation, there is considerable variability in the response to vasodilatory stimuli among persons with the same number of coronary risk factors, particularly in the intermediate range (Vita et al., 1990). It is possible that, as with other cardiovascular responses, psychological variables account for some of that variance.

Hostility and Cardiac Events. Hostility is an extensively investigated psychological variable that may contribute to variance in cardiovascular events among persons with the same cardiovascular risk factors. Hostility has been described as a mixture of anger and disgust and is associated with emotions such as resentment, indignation, and contempt. Hostility is often accompanied by anger and may carry with it an element of destructiveness (Diamond, 1982). Hostility is often measured by a scale derived from the Minnesota Multiphasic Personality Inventory (MMPI) by Cook and Medley (Cook & Medley, 1954). As measured by Cook-Medley Hostility Scale total scores, hostility has been reported to predict mortality from cardiovascular diseases (Barefoot, Dahlstrom, & Williams, 1983; Shekelle, Gale, Ostfeld, & Paul, 1983). Further, hostility predicts the severity of myocardial ischemia in patients with cardiac disease (Burg, Jain, Soufer, Kerns, & Zaret, 1993). Hostility also predicts recurrent events, such as myocardial infarction and sudden cardiac death, in CAD patients (Powell & Thorenson, 1985), although results in this domain have been mixed.

However, even in light of these studies showing positive associations between

hostility and cardiovascular events, other studies have found no association between hostility and cardiovascular disease (e.g., McCranie, Watkins, Brandsma, & Sisson, 1986). The McCranie, et al. (1986) study was nearly identical to a prior study which yielded a positive association between hostility scores and cardiovascular disease (Barefoot, Dahlstrom, & Williams, 1983). It differed, though, in that the participants in the McCranie, et al. (1986) study were given the Cook-Medley only once when they entered medical school. Barefoot and colleagues (1983) tested their participants twice over a span of several years in order to determine the reliability of the hostility scores obtained upon entrance to medical school. It may be that the scores of the participants in the McCranie, et al. (1986) study merely reflect hostile attitudes associated with entering a highly competitive environment and not a persistent pattern of behavior. Nevertheless, approximately a third of studies examining hostility and cardiovascular disease fail to find an association between hostility and cardiovascular endpoints, and explanations for some of these negative findings are not immediately apparent (e.g., Hearn, Murray, & Luepker, 1989).

Components of Hostility. In an attempt to determine why some studies of hostility and cardiovascular disease yield positive associations while others do not, Barefoot and colleagues derived subscales from the Cook-Medley scale using the face validity of the items and theories of aggression, attitudes, and information processing (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989). They first divided items between behavioral and experiential items; that is, those that represent acts of coercion designed to achieve an external goal and those motivated by anger. Within the experiential domain, items were further separated into statements of belief and those that reflect the experience of emotion. Items that represented beliefs were again separated into items that represent the

tendency to interpret behavior of others as intended to harm the respondent and those that represent a generally negative view of humankind not necessarily directed at the respondent. These two subdivisions were labeled Hostile Attributions and Cynicism, respectively. Those items that referred to the experience of negative emotions associated with social relationships were labeled Hostile Affect. Aggressive Responding refers to items regarding the respondent's tendency to use anger and aggression as instrumental responses to problems or to endorse these behaviors as reasonable and justified. Finally, Social Avoidance refers to indirectly negative behaviors that indicate the respondent's tendency to avoid others, refrain from social interaction, or withdraw from personal involvement (e.g., "I am not likely to speak to others unless they speak to me first").

Barefoot and colleagues (1989) then followed up 128 law students who took the Minnesota Multiphasic Personality Inventory (MMPI) during law school in 1956. Cynicism, Hostile Affect, and Aggressive Responding were significant predictors of survival, whereas the Hostile Attribution and Social Avoidance subscales were not. The sum of the three predictive subsets yielded a chi-square nearly 50% larger than that produced by the full hostility scale ($\chi^2 = 6.37$, $p = 0.012$ vs. $\chi^2 = 9.45$, $p = 0.002$). The authors suggested that these three subscales are more predictive than the full hostility scale because their combination forms a theoretically coherent triad. That is, the Cynicism items are statements of belief, Hostile Affect items refer to emotional experiences, and Aggressive Responding refers to overt behavior. Barefoot, et al. (1989) suggest that the Hostile Attribution and Social Avoidance subscales are less predictive and may simply add "noise" that attenuates the predictive value of total Cook-Medley scores.

Cardiovascular Reactivity. One mechanism by which hostility and other

psychological variables may promote cardiovascular disease is cardiovascular reactivity (e.g., Burns & Katkin, 1993; Krantz & Manuck, 1984). Cardiovascular reactivity refers to the response of the cardiovascular system to stress. Measures of reactivity may include heart rate, blood pressure, and other cardiovascular responses. It is generally defined in terms of change scores independent from resting levels (Krantz, Helmers, Bairey, Nebel, & Rozanski, 1991). Persons with high levels of anger and hostility significantly exceed persons with low levels on cardiovascular reactivity to mental stress testing (Weidner, Friend, Ficarrott, & Mendell, 1989; Burns & Katkin, 1993).

Studies have shown that higher levels of reactivity to mental stress predict cardiac symptoms as well as future development of cardiovascular disease, perhaps due to hormonal changes and/or increased demand on the heart (e.g., Schneiderman, et al., 2000). Mental arithmetic, a commonly used mental stress testing procedure ( e.g., Specchia, et al., 1984), has been shown to increase total body norepinephrine spillover by 53% and cardiac norepinephrine spillover by 160%, from a mean of 12.2 to a mean of 19.52 (Meredith, Esler, Eisenhofer, & Jennings, 1990). Mental arithmetic and other mental stress tasks reliably increase systolic and diastolic blood pressure and, to a lesser degree, heart rate (e.g., Kamarck, et al., 1992).

Cardiovascular reactivity has been associated with development of cardiovascular disease as well as symptoms and events in persons who have coronary disease. Higher levels of cardiovascular reactivity are associated with increased risk for atherosclerosis in animals (Manuck, Kaplan, & Clarkson, 1983), and diastolic blood pressure reactivity during cold pressor testing is predictive of future development of coronary artery disease in humans (Keys, et al., 1971). Mental arithmetic and public speaking tasks both induce transient myocardial ischemia in 30-60% of CAD patients (Rozanski, et al., 1988).

Patients exhibiting severe ischemia during mental stress have greater systolic blood pressure responses to mental stress than do other patient groups or controls (Krantz, Helmers, Bairey, Nebel, & Rozanski, 1991). Mental stress testing may also result in perfusion abnormalities (Deansfield, et al., 1984), reduced ejection fraction (Ironson, et al., 1992), and in rare cases, ST-segment depression, which is an indicator of myocardial ischemia (Barry, et al., 1988), and angina (Yeung, et al., 1991). These cardiovascular changes may be due to increases in blood pressure and catecholamine secretion (Rozanski, et al., 1988). However, mental stress testing can produce an absolute decrease in regional blood flow in addition to the increase in heart rate and blood pressure. Angiographically smooth arteries usually either do not change or dilate in response to mental stress, whereas irregular and stenosed vessels constrict. In normal arteries, mental stress produces an increase in coronary blood flow. In the presence of atherosclerosis, regional coronary blood flow decreases, despite a similar increase in heart rate, blood pressure, and plasma norepinephrine levels (Yeung, et al., 1991). Endothelial dysfunction may play a role in the cardiac symptoms induced by mental stress.

Noninvasive Assessment of Endothelial Function. The present study sought to determine the effects of hostility and mental stress on endothelial function. Endothelial function has previously been studied using invasive techniques. However, these techniques are inappropriate for the investigation of early endothelial dysfunction in young, asymptomatic individuals. Celermajer and colleagues (1992) developed a reliable, noninvasive technique for measuring endothelial function in relatively large, superficial arteries (e.g., femoral, brachial, corotid) using high frequency, two-dimensional ultrasound (see also Sorenson, et al., 1995).

Endothelial function can be measured noninvasively using the response of blood

vessels to increases in blood flow. It has been demonstrated that the endothelium is responsible for the vasodilator response to increased flow (Pohl, Holtz, Busse, & Bassenge, 1986; Rubanyi, Romero, & Vanhouette, 1986; Laurent, Selwyn, & Ganz, 1990). Perhaps the simplest way to increase flow *in vivo* is to induce reactive hyperemia using short-term occlusion. Preliminary evidence suggests that the increase in shear stress produced by increased flow may release nitric oxide through the activation of potassium ion channels (Anderson, et al., 1995). It could be argued that arterial dilation following occlusion may result from the effects of ischemic metabolites. However, although ischemic metabolites are produced during occlusion, it is unlikely that they directly dilate blood vessels because dilation occurs a number of seconds after the release of arterial occlusion, a time when concentrations of ischemic metabolites are decreasing (Sinoway, Hendrickson, Davidson, Prophet, & Zelis, 1989).

It has been demonstrated that the magnitude of endothelium-dependent arterial dilation is inversely correlated with the baseline diameter of the artery (Celermajer, et al., 1992; Anderson, 1995). In order to avoid a ceiling effect, studies using the Celermajer method to evaluate endothelial function in adults are best performed on smaller arteries such as the brachial artery as opposed to the larger femoral artery. The brachial artery increases in diameter in a graded fashion as blood flow increases. The increase in diameter occurs later than the restoration of blood flow, and the artery remains dilated for a time after flow has returned to baseline (Sinoway, Hendrickson, Davidson, Prophet, & Zelis, 1989).

Endothelial responses in the brachial artery were initially reported to correlate moderately with endothelial responses in coronary arteries ($r = .31$; Anderson, 1995). However, Anderson and colleagues (1995) infused acetylcholine to provoke endothelial

responses in coronary arteries and increased flow to cause vasodilation in brachial arteries. In a later study which used the same stimulus (increased flow) in both coronary and brachial arteries, the correlation between coronary endothelial responses and brachial artery endothelial responses was much higher ($r = .78$, $p < .001$; Takase, et al., 1998).

Brachial artery endothelial dysfunction has also been positively associated with cardiovascular risk factors, including smoking, gender, positive family history for cardiovascular disease, hypertension, and high cholesterol (Celermajer, et al., 1992; Heitzer, et al., 1996; Panza, Quyyumi, Brush, & Epstein, 1990; Anderson, 1995). Evidence suggests that the brachial vasodilator dysfunction parallels progressive coronary endothelial dysfunction, making it a good indicator for coronary endothelial function (Anderson, 1999; Takase, et al., 1998).

Study Purpose and Hypotheses. The purpose of the present study was to examine the effects of mental stress on endothelial function in the brachial artery using high-resolution ultrasound. To examine mediators of mental stress-induced brachial artery vasomotion, we examined the role of stress-induced blood pressure elevations and the possible effects of the components of hostility on endothelial function. Specifically, this study addressed the following hypotheses:

1. Mental stress will cause endothelial-dependent dilation of the brachial artery. It is well documented that reactive hyperemia induces endothelial-dependent dilation via increased shear stress (e.g., Pohl, Holtz, Busse, & Bassenge, 1986). It is, therefore, hypothesized that the increased blood pressures associated with mental stress will similarly increase shear stress and cause endothelial-dependent vasodilation in the brachial artery.

2. Mental stress and occlusion combined will result in increased vasodilation compared to occlusion alone in healthy individuals. It is further hypothesized that mental-stress induced blood pressure increases add to the shear stress of reactive hyperemia, placing greater demand on the endothelium, and thereby exacerbating any endothelial dysfunction that might exist in individuals with risk factors for cardiovascular disease.
3. Cynicism, Hostile Affect, and Aggressive Responding will predict endothelial responses. Based on the findings of Barefoot and colleagues (1989) that the Cynicism, Hostile Affect, and Aggressive Responding subscales of the Cook-Medley are better predictors of cardiovascular outcomes than total Cook-Medley scores, it is hypothesized that Cynicism, Hostile Affect, and Aggressive Responding will be associated with impaired brachial artery vasodilation in response to hyperemia, mental stress, and in particular, the combination of mental stress and hyperemia because detection of endothelial dysfunction is hypothesized to be most sensitive in the latter (combined) situation.

## METHODS

### Participants

Participants were recruited from the Baltimore-Washington, D.C., area for a study examining the effects of cholesterol and mental stress on endothelial function. Participants were made aware of the study via flyers, word of mouth, and referrals from their primary care physician. Persons with cardiac arrhythmias, CAD, congestive heart failure, and known psychiatric disorders were excluded from the study. A total of 46 participants were recruited, and individuals with hyperlipidemia were oversampled. *A*

*priori* power analysis revealed that 40 subjects are required to detect differences between hostile and non-hostile individuals with a power of > 80% and alpha set at 0.05, if data are analyzed using a median split (comparing hostile versus non-hostile participants). Forty subjects are also more than sufficient to detect differences from baseline with regard to endothelial responses to hyperemia, mental stress, and hyperemia and mental stress combined (e.g., Celermajer, et al., 1992), using a Bonferoni corrected alpha of 0.013 (i.e., 0.05/4).

The first six participants served as pilot subjects so that the ultrasound technician could refine the very precise technique required to yield usable data from examination of the brachial artery. Ultrasound data were recorded onto VHS videocassettes and analyzed in a core lab at Wake-Forest University. After the core lab determined that the protocol was producing valid data, the remaining 40 subjects were run.

After completing the laboratory protocol, participants took psychological questionnaires home to be returned in a postage-paid envelope after they had been completed. However, some subjects moved, lost the questionnaires, or simply failed to complete them even after several reminders. Of the 40 participants with usable ultrasound data, 28 returned their psychological questionnaires, resulting in a sample of 17 women and 11 men. The mean age was 42 +/- 17 years, and mean education level was 16 +/- 2 years. Participants were 78% Caucasian, 11% African American, and 11% Asian. Eight percent were current smokers, and 54% were former smokers. Fourteen percent were hypertensive, and 46% were hypercholesterolemic (See table 1).

Procedure

The present study was approved by the Internal Review Boards at the Uniformed Services University and the Georgetown University Medical Center. Participants

completed a protocol in which each individual completed four tasks: forearm occlusion, mental stress, combined mental stress and occlusion, and nitroglycerin. Because there is high variability in endothelial responses between individuals, and because the absolute change in the brachial artery is small, a within-subject design was chosen so that each individual served as his or her own control.

Each intervention lasted 4 minutes. High-resolution ultrasound images of the brachial artery were taken above the right elbow in longitudinal section during all conditions (Celermajer, et al., 1992). Images were acquired during all 4 minutes of each condition and for 2 minutes following the completion of each condition. Blood pressure measurements were taken every 2 minutes throughout the protocol using an automated blood pressure cuff (Dinamap XL Vital Signs Monitor UL/CSA, Critikon, Johnson & Johnson Medical, Inc).

After providing informed consent, participants were given an overview of the study and a demonstration of the ultrasound procedure. An automatic blood pressure cuff was placed on the participant's left arm, and he or she was instructed to lie in the supine position. The lights were then dimmed, and the participant was instructed to relax for 10 minutes. Baseline measurements were taken during the last four minutes of the rest period. The four interventions then followed with ten minute resting periods between each of them.

Occlusion. Occlusion served as a control condition during which unadulterated endothelial function was evaluated (Laurent, Selwyn, & Ganz, 1990). In the occlusion condition, a pneumatic blood pressure cuff was inflated on the participant's right forearm to 50 mmHg higher than her or her resting systolic blood pressure (Sinoway, Hendrickson, Davidson, Prophet, & Zelis, 1989). The cuff remained inflated for 4

minutes and then was released.

Mental stress. During a mental stress condition, the participant either gave an anger-provoking speech (Ironson, et al., 1992; Carney, et al., 1997) or subtracted serial sevens from a four digit number while being prodded by the experimenter to be quick and accurate (Specchia, et al., 1984; Patterson, Krantz, & Jochum, 1995). Each participant completed both the speech and the math task, either with occlusion or alone. Half the participants were randomly assigned to complete the math task combined with occlusion and the speech task by itself. The other half completed the speech task combined with occlusion and the math task by itself. Cardiovascular responses to particular mental stress tasks generally attenuate after 4 minutes (e.g., Kamarck, 1992). A different task had to be administered during each of the mental stress conditions because each task becomes considerably less effective upon repetition. Participants were instructed to remain still while talking to the experimenter in order to prevent disruption of the ultrasound image.

Combined mental stress and occlusion. In the combined condition, a pneumatic blood pressure cuff was inflated on the forearm for 4 minutes as described in the occlusion condition. While the cuff was inflated, the participant completed the mental stress task that he or she did not do during the mental stress condition.

Nitroglycerin. Sublingual nitroglycerin (0.4mg) was administered by a physician for the purpose of evaluating the participant's endothelial-independent vasodilation. Ultrasound images were taken when nitroglycerin was administered and for the following 6 minutes. Participants then rested for 10 minutes or until their blood pressures returned to baseline.

The occlusion, mental stress, and combined conditions were counterbalanced for order, but nitroglycerin was always given last because of its longer-lasting effects.

Further, the two types of mental stress tasks were counterbalanced between the mental stress conditions. After the laboratory session, a psychological battery including the Cook-Medley Hostility Scale and the Profile of Mood States (POMS) was administered. Both the Cook-Medley and the POMS have been demonstrated to be reliable instruments and show convergent and divergent validity (Cook & Medley, 1954; Smith & Frohm, 1987; McNair, Lorr, & Droppleman, 1992).

## RESULTS

Differences between groups and predictors of brachial responses are first analyzed using bivariate correlations and *t*-tests with a combined alpha level of 0.05 for questions involving two levels of the independent variable. Questions involving three or more levels of the independent variable were analyzed using Analysis of Variance (ANOVA). Differences and associations that were significant at the univariate level were subsequently analyzed using a multiple regression stepwise procedure in order to control for possible confounding of covariates such as baseline diameter, blood pressure, age, sex, and cholesterol levels.

Efficacy of interventions. Brachial artery diameter increased significantly from baseline during occlusion, mental stress, occlusion and mental stress combined, and nitroglycerin (See figure 1 and table 2). All participants' brachial arteries dilated during all interventions. That is, no one constricted or remained the same. Task order effects were controlled via counterbalancing. Brachial artery response to mental stress was associated with age ($r = -.51$, $p < .0001$) and smoking status ($t = 3.7$, $p = .001$). Smokers had attenuated responses to mental stress compared to nonsmokers, and older individuals did not dilate as much as younger individuals. Brachial responses were not associated with gender or smoking status during occlusion, occlusion and mental stress

combined, or nitroglycerin. Artery responses also did not significantly correlate with hypertensive status or education in any condition. Race was associated with vasomotor responses during mental stress ($F = 4.08$, $p = .03$) and the combined condition ($F = 4.65$, $p = .02$), but not during occlusion alone. Caucasians dilated more than African Americans during the mental stress and occlusion combined condition ($t = 3.11$, $p = .005$), and Asian Americans dilated more than Caucasians during both mental stress ($t = 2.57$, $p = .02$) and the combined condition ($t = 2.76$, $p = .01$).

Systolic blood pressure, diastolic blood pressure, and heart rate increased during mental stress and combined mental stress and occlusion (See figure 2 and table 3). Systolic blood pressure, diastolic blood pressure and heart rate did not increase during occlusion alone. Blood pressure decreased significantly during nitroglycerin ($t = 5.3$, $p < .0001$).

Baseline artery diameter. Gender was associated with baseline artery diameter in that women had smaller arteries than men ($t = 3.8$, $p = .001$). Baseline diameter was not associated with race, cholesterol, age, education, hypertension, or smoking status. No hostility measures were significantly associated with brachial artery baseline diameter for any condition.

Hostility and Components of Hostility. Hostility measures were not significantly associated with brachial artery vasomotion during occlusion, mental stress, or nitroglycerin. However, during the mental stress and occlusion combined, Hostile Affect was significantly associated with change in brachial artery diameter ($r = -.57$, $p = .002$). There were similar nonsignificant trends for Cynicism and Cook-Medley total scores ($r = -.31$, $p = .13$; $r = -.32$, $p = .13$, respectively; $r^2 = .096$ and .103). Because psychological variables generally only account for 25% of the variance in cardiac outcomes,

psychological measures that account for 9-10% of the total variance are clinically relevant even in the absence of statistical significance. The Anger-Hostility scale of the POMS was similarly related to change in artery diameter in the combined condition ($r$ = -.34, $p$ = .08; see table 4 and figures 3 and 4). Because hostility was not significantly associated with brachial artery endothelial function during occlusion or mental stress alone, regression analysis was performed only on the combined condition.

Regression analysis of hostility data during combined condition. Data were analyzed using forward step-wise multiple regression with the univariate predictors of brachial response entered first. After controlling for age, sex, race, baseline diameter, and blood pressure responses to tasks, Hostile Affect remained a significant predictor of brachial artery response ($\beta$ = -.545, $t$ = 2.5, $p$ = .02; see table 5).

## DISCUSSION

Consistent with prior literature, mental stress induced dilation of the brachial artery in normal participants. However, in this study, cardiovascular risk factors, including hypertension, smoking status, and race, were not associated with the degree or direction of change in the endothelial-dependent vascular response to mental stress. This lack of association may be due to insufficient power to detect effects of risk factors other than age, gender, and hypercholesterolemia. In addition, the present sample was relatively young, and few participants had risk factors other than hypercholesterolemia, and those risk factors that were present were generally moderate (e.g., mild hypertension.) The present study did reveal significant associations between components of hostility and endothelial dysfunction in the condition of mental stress and hyperemia combined. Prior research suggests that participants with more severe risk factors would yield higher effect sizes (e.g., Celermajer, et al., 1990; Heitzer, et al., 1996; Vita, et al.,

1990).

Women had smaller brachial arteries than men; however, brachial responses to occlusion, mental stress, and the combined condition did not differ between men and women after statistically controlling for baseline diameter. Vasodilatory responses were related to race. As in prior studies (e.g., Woo, et al., 1997), Asian Americans had greater brachial artery responses than Caucasian or African Americans. This difference may be due to the fact that, in this sample, Asian Americans had lower cholesterol levels and lower body mass index scores than other ethnic groups.

Mental Stress and Occlusion Alone Compared to the Combined Condition

None of the hostility measures were related to brachial artery response to mental stress alone or occlusion alone. However, during the combined condition, Hostile Affect and the Anger-Hostility scale of the POMS were associated with percent change in brachial artery diameter, even after statistically controlling for traditional components of cardiovascular reactivity (i.e., blood pressure and heart rate). The fact that hostility variables are associated with arterial dilation in response to mental stress and occlusion combined, but not with responses in either condition alone, suggests that both conditions were required to elicit an effect, perhaps because any endothelial dysfunction present in this sample was incipient (i.e., in the early stages) and required the compounded shear stress of increased blood pressure and reactive hyperemia for attenuated dilation to manifest to a statistically significant degree. Perhaps the increased flow due to reactive hyperemia or increased blood pressures in response to mental stress alone were insufficient to provoke an attenuated response in persons with impaired endothelial function in this sample. This finding also suggests that, in this sample, the combined effects of mental stress and reactive hyperemia interacted in some way to elicit attenuated

endothelial responses. Whether they interacted in an additive or multiplicative way cannot be determined from the present study and should be examined in studies with a greater number of participants.

A study published after the collection of the present data ($n$ = 20) reported that mental stress alone cause transient endothelial dysfunction in normal individuals (Ghiadoni, et al., 2000). However, in that study, endothelial-dependent dilation was attenuated 30 and 90 minutes after administration of the mental stress task, suggesting that mental stress may interfere with endothelial-dependent dilation after mental stress, rather than during mental stress.

Hostile individuals, particularly those with higher scores on the Hostile Affect subscale of the Cook-Medley, have a reduced brachial vasodilatory response to the combined challenge of mental stress and flow-mediated hyperemia compared to non-hostile individuals, which suggests that their vascular endothelial function is impaired. It has been demonstrated that impaired endothelial functioning is associated with cardiovascular disease (e.g., Anderson, 1995) and can result in paradoxical coronary vasoconstriction under stressful conditions (e.g., Nabel, et al., 1988). The findings of this study may help to explain the fact that hostile individuals are more likely to experience myocardial ischemia in response to mental stress (e.g., Burg, et al., 1993).

Hostile Affect

It is of interest that the affective components of both the Cook-Medley and the POMS were the only significant psychological predictors of endothelial-dependent vasodilation. Apparently, it is the emotional aspect of hostility (rather than cognitive or behavioral aspects) that is most highly associated with vascular endothelial dysfunction. Further study with a larger sample is needed to determine whether or not the other two

components of Barefoot and colleagues' triad (i.e., Cynicism and Aggressive Responding) are predictive of endothelial dysfunction in addition to other types of cardiovascular morbidity. Power analyses indicate that approximately 80 participants would be required to reveal significant associations for Cynicism and Aggressive Responding when data are analyzed using correlation techniques. Correlation statistics were the most appropriate for the current data.

If future investigations bear out the association between hostile affect and endothelial function but fail to find an association between cynicism or aggressive responding and endothelial function, then it may be worth examining the concept of emotional responsivity. It has not yet been demonstrated whether hostility is causally associated with cardiovascular disease or whether hostility influences cardiovascular symptoms and outcomes by evoking negative emotional states (Krantz, et al., 1991). Carels and colleagues (1999) have suggested that emotional responsivity may be responsible for the cardiac symptoms that can be evoked by mental stress in the lab and in daily life. It may be that it is not trait hostility, but rather hostile emotions that are evoked by mental stress in persons who are generally emotionally responsive, that caused attenuated endothelial responses in this study. Future studies should include a measure of general emotional responsivity and perhaps a measure of plasma catecholamine levels in order to determine which individuals have greater stress responses during the laboratory tasks and whether they are the ones who dilate less. However, it should be noted that, in the present studies, individuals with higher hostility scores did not report being angrier, more irritated, more frustrated, or more challenged during the mental stress tasks than those with lower hostility scores.

It may also be simply that the emotional component of a hostile response is the

most likely to trigger an adverse cardiovascular response. It has been reported that emotional responses can elicit cardiovascular responses as large as those that occur with exercise (e.g., Ironson, et al., 1992)

It should be noted that this study is limited by its small sample size given the fact these data were best analyzed using correlational techniques. Based on the effect sizes obtained in this study, we conducted additional *post-hoc* power analyses, which revealed that approximately 80 participants with the characteristics of the present sample (age, risk factors, sex, race) would be required to detect group differences (high versus low hostile) on endothelial dysfunction as objectified by assessment of hyperemia responses alone. Further studies should be conducted on larger sample sizes since the absolute change in brachial artery size under any circumstances is fairly small. Investigations of the relationship between risk factors and endothelial function during mental stress should include a greater number of participants with the relevant characteristics, including hyperlipidemia, hypertension, and high hostility levels. In addition, studies should be run on more heterogeneous samples, because it has been demonstrated in this and other studies that race affects endothelial function (e.g., Woo, et al., 1997).

Future investigations are needed to determine the mechanism of the effect of hostility or hostile emotions on endothelial function. Developmental studies may also be helpful to determine causality and to discover when in the developmental process hostility begins to become associated with endothelial function. Because endothelial dysfunction begins to occur as young as age eight in children with traditional cardiovascular risk factors, psychological risk factors may have an impact in childhood as well. Studies should confirm that the vascular response to mental stress is indeed due to the release of nitric oxide and should investigate the possibility of other mechanisms.

Finally, future studies should further explore the interaction between the activation of the sympathetic nervous system and the endothelial response to mental stress. It may be that the reason hostility becomes associated with endothelial function only during the occlusion and mental stress combined condition is that some interaction between the sympathetic nervous system and the flow-mediated release of nitric oxide exacerbates any underlying endothelial dysfunction. This hypothesis could also be explored in future studies by including a measure of catecholamines to determine whether greater sympathetic activation results in attenuated flow-mediated endothelial responses.

## Participant Characteristics

| | Men | Women |
|---|---|---|
| Sex | 11 | 17 |
| Age | 33 +/- 10 years | 47 +/- 13 years |
| Race | 63% Caucasian, 18% African American, 18% Asian | 88% Caucasian, 6% African American, 6% Asian |
| Education | 15 +/- 1.7 years | 16 +/- 2 years |
| Cholesterol | 18% > 200 mg/dl | 53% > 200 mg/dl |
| Smoking status | 18% current, 54% former | 0 current, 82% former |
| Hypertensive | 18% (current) | 12% (current) |

**Table 1**

## Brachial Artery Response to Interventions

| Condition | Mean difference (mm) | *t* | SD | *p* |
|---|---|---|---|---|
| Occlusion | .16 | 10.55 | .08 | < .0001 |
| Mental stress | .15 | 7.39 | .10 | < .0001 |
| Occl + MS | .15 | 9.27 | .07 | < .0001 |
| Nitroglycerin | .49 | 16.34 | .14 | < .0001 |

**Table 2** Occl = Occlusion; MS = Mental Stress

## Blood Pressure and Heart Rate Response to Interventions

| | Mean difference (mmHg) | *T* | SD | *p* |
|---|---|---|---|---|
| Occlusion SBP | .84 | 1.0 | 4.4 | NS |
| Occlusion DBP | .03 | .04 | 3.9 | NS |
| Occlusion HR | .08 | .10 | 4.1 | NS |
| Mental stress SBP | 18.9 | 10.0 | 9.8 | < .0001 |
| Mental stress DBP | 12.3 | 8.3 | 7.7 | < .0001 |
| Mental stress HR | 11.4 | 8.0 | 7.4 | < .0001 |
| Occl + MS SBP | 18.2 | 7.6 | 12.4 | < .0001 |
| Occl + MS DBP | 11.5 | 9.8 | 6.1 | < .0001 |
| Occl + MS HR | 12.3 | 8.2 | 7.8 | < .0001 |

**Table 3** SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate

Zero-order Correlations

| | Occlusion | Mental Stress | Occlusion + MS |
|---|---|---|---|
| Cook-Medley total | .03 | .17 | -.32 |
| • Cynicism | -.04 | .22 | -.31 |
| • Hostile Affect | -.15 | -.15 | -.57** |
| • Aggressive Responding | .07 | .13 | -.08 |
| Anger-Hostility (POMS) | .09 | .32 | -.34* |

**Table 4**

*$p < .01$, **$p < .001$

Regression Analysis of Hostility Variables during Mental Stress and Occlusion Combined

| | | SE | *t* | *p* |
|---|---|---|---|---|
| Age | .002 | .032 | .66 | .52 |
| Sex | -.141 | 1.13 | .13 | .90 |
| Blood pressure | .003 | .02 | 1.49 | .16 |
| Race | .599 | .26 | 2.35 | .03 |
| Baseline Diameter | -.358 | .56 | .64 | .53 |
| Hostile Affect | -.55 | .22 | 2.50 | .02 |

**Table 5**

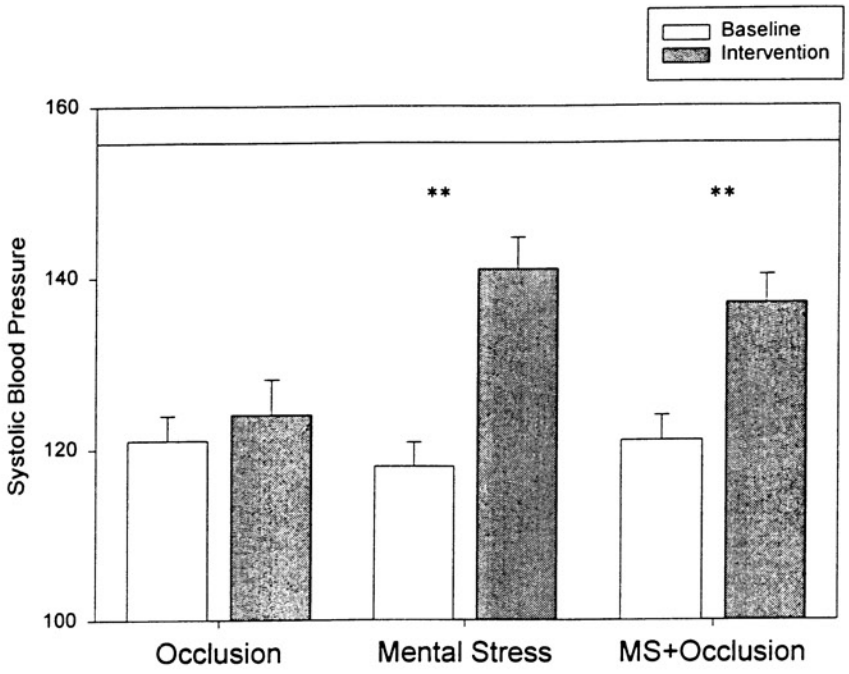


Figure 1

** $p < .001$

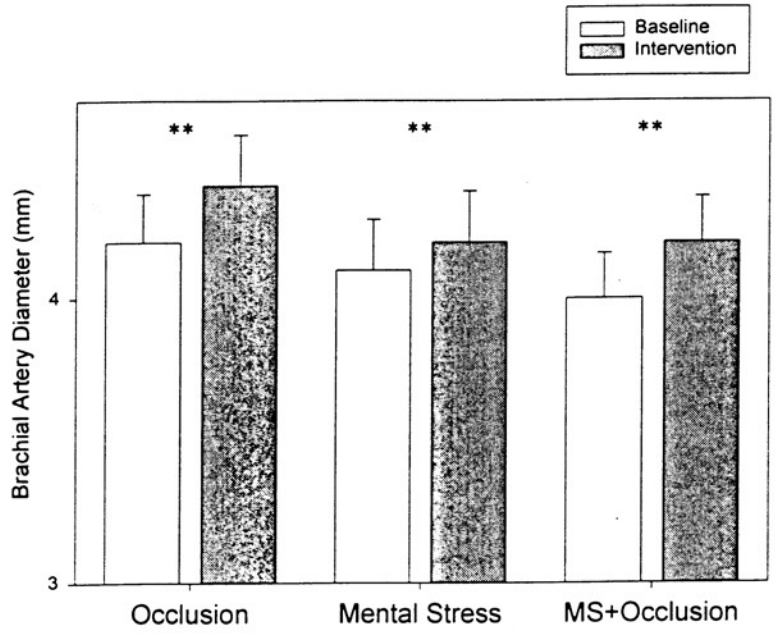


Figure 2

** $p < .001$

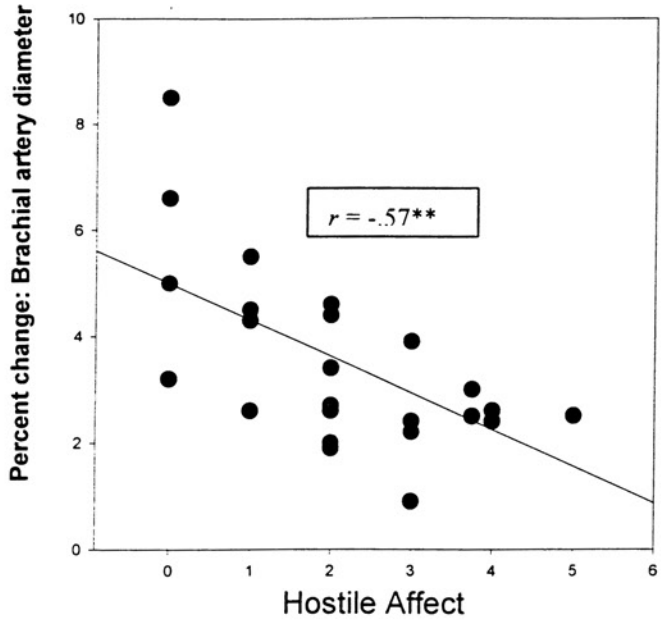


Figure 3 ** $p < .001$

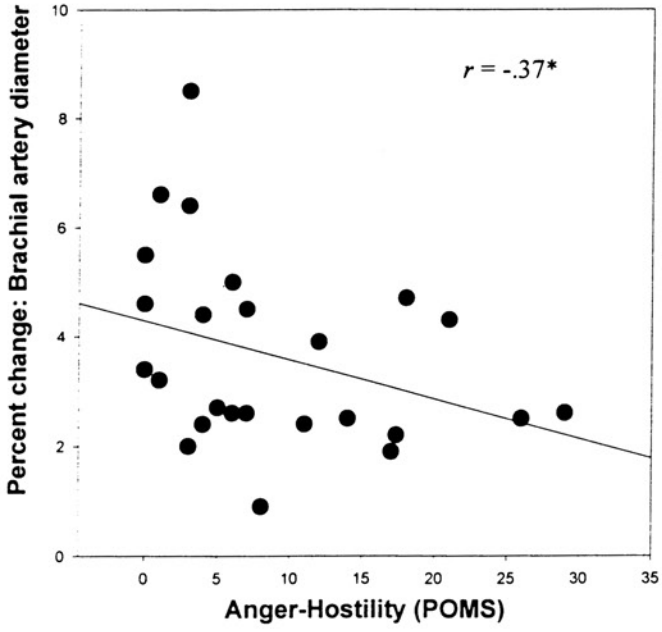


Figure 4 * $p = .08$

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